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14. ABSTRACT People differ in their susceptibility to abuse alcohol and drugs, and the conditions that lead to abuse and dependence are not the same in everyone. Some people are susceptible because they experience particularly positive effects from alcohol and drugs; often, the same people have problems controlling their behavior. They are impulsive; they seek out novel and exciting experiences; and they may be influenced by other rewards, such as those associated with gambling or risky sexual behavior, even if the long-term consequences of those behaviors are harmful. This study will evaluate the relationship between the response to a stimulant drug and behavioral control. First, we will administer 10 mg *d*-amphetamine and select groups of individuals with distinct stimulant responses to that drug. Next we will record event-related brain potentials (ERPs) while participants perform tasks that tap aspects of behavioral control: response inhibition, novelty detection, and reward processing. To evaluate the neural mechanisms involved in these processes, we will record ERPs after placebo, and in a separate session, after 10 mg *d*-amphetamine. This research will identify aspects of control that differentiate these groups and elucidate the neural systems that mediate these differences. As such, the findings of this research may lead to better treatments for alcohol and drug abuse, particularly for people who abuse these drugs because of their stimulating effects.

15. SUBJECT TERMS
event-related brain potentials (ERPs), stop P3, error-related negativities, P300, P3a, reorienting negativity (RON), response inhibition, reward processing, novelty detection, error-processing, vulnerability marker, cognitive control, amphetamine

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PR065029 Cooperative Agreement

Amphetamine Challenge:
A Marker of Brain Function that Mediates Risk for Drug and Alcohol Abuse

Principal Investigator: Frances H. Gabbay, Ph.D.

Annual Report (No. 3)

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Introduction

People differ widely in their susceptibility to abuse alcohol and other drugs, and the conditions that lead to abuse and dependence may not be the same in all people. Some people are susceptible because they experience particularly positive effects from alcohol and drugs—the drugs make them feel good. Often, the same people who experience these very positive effects also have problems controlling their behavior. They are impulsive—it may be difficult for them to stop a behavior, even if they realize it could lead to a bad outcome. They seek out novel and exciting experiences, often without considering the consequences, and are often influenced by other rewards. They do things that may lead to short-term rewards, such as gambling or risky sexual behavior, even if the long-term consequences may be harmful. When these characteristics occur together, individuals are more likely to try alcohol or drugs at a young age, to use these substances more heavily, to continue their use, and to develop problems related to their use. We do not know why some people experience more positive—or stimulating—effects of alcohol and drugs, or why this characteristic is sometimes associated with poor control. Using cognitive tasks that invoke specific aspects of behavioral control, it is possible to assess in the laboratory aspects of behavioral control related to risk for alcohol and drug abuse. Event-related brain potentials (ERPs) recorded during performance of these tasks permit evaluation of concomitant neural processing. Thus, in the first phase of this study, we administer to young men and women 10 mg *d*-amphetamine, a drug with stimulant effects that are similar to those of alcohol and other drugs. We record the effects of the drug on their mood, and select groups of people who experience distinct stimulant responses to this dose of *d*-amphetamine. Then, in two separate sessions, we record ERPs while individuals in the different responder groups perform tasks designed to tap aspects of behavioral control: response inhibition, novelty detection, and reward sensitivity. In one of the two sessions, we administer a placebo; in a separate session, we administer 10 mg *d*-amphetamine. The research will identify aspects of behavioral control that are associated with the stimulant drug response, and elucidate the cognitive and neural bases of these differences. The results of this study will help us to understand the association between stimulant drug response and behavioral control (i.e., why they occur together in people and how they lead to poor decisions about alcohol and drug use). Thus, the findings of this research may lead to better treatments for alcohol and drug abuse, particularly for people who abuse these drugs because of their stimulating effects, and who make impulsive decisions about using these substances.

Body: Progress and Problems

Progress

In this section, we state progress made in terms of the tasks in our *Statement of Work*. We obtained Human Subjects Research Review Board (HSRRB) approval on 7/03/08, for the protocol as well as for amendments that reflect improvements to the original protocol. The latter were detailed in our first annual report. In the time since obtaining approval, we have focused on recruiting, screening, and testing participants, and on processing data collected during the testing.

Task 1: Submit protocol to local (USU) Institutional Review Board (IRB). **DONE**
a. Develop and submit protocol, informed consent documents, and other supporting materials, including questionnaires and other study forms, to IRB.
b. Provide IRB approval letter to USAMRAA.

Task 2: Submit protocol to USAMRMC HSRRB and obtain HSRRB approval. **DONE**

Task 3: Engineer modifies software to meet study specifications. **DONE**

Task 4: Preparations for testing. **DONE**
a. Recruit research assistants.
b. Recruit nurse practitioner.
c. Train research assistants in all procedures for the study.
d. Order laboratory supplies and set up laboratory.

Task 5: Recruitment and screening. **IN PROGRESS**
a. Place advertisements **CONTINUOUS**
b. Field responses to advertisements **CONTINUOUS**

Task 6: Conduct web-screening of 2,725 participants. **DONE**
a. Review interviews to determine eligibility for health screening
b. Schedule eligible participants for health screening

Task 7: Conduct health screening for 506 participants. **DONE**
a. Conduct 20-21 health screening sessions per week
b. Review test and interview results to determine eligibility for physical exam
c. Schedule eligible participants for physical examinations
d. Begin to track menstrual cycle of all eligible women

Task 8: Conduct physical exams of 186 participants. **DONE**
a. Conduct 8–9 physical examinations per week
b. Review results of exam to determine eligibility for medication-response testing
c. Schedule eligible participants for medication-response testing

Task 9: Conduct medication-response (BAES screening) sessions for 186 participants. **IN PROGRESS (170/186 completed)**

a. Conduct medication-response session for 8-9 participants per week
b. Score BAES and identify participants eligible for ERP testing, using criteria in proposal
c. Schedule eligible participants for ERP testing sessions
d. Nurse practitioner continues to track menstrual cycle of all eligible women.

Task 10: Test 96 participants in two ERP sessions each. **IN PROGRESS (92/96 completed)**
a. Conduct 7-8 ERP sessions per week
b. Ensure that a minimum of 48 h intervenes between the two ERP sessions for each participant

c. Nurse practitioner continues to track menstrual cycle of all eligible women until they complete two ERP sessions

Task 11: Process ERP data from first 192 ERP sessions (96 participants). **IN PROGRESS**
a. Back up data from each testing session, as described in the proposal
b. Execute blink correction algorithm, as described in proposal
c. Average ERP data for each participant within 24 h of testing session
d. Quantify ERP data for each participant within 72 h of testing session
e. Plot averaged ERP waveforms for each participant
f. Investigators review plots and quantified data for each participant

Task 12: Conduct preliminary analysis of ERP data. **DONE**

Task 13: Score BAES and prepare graphic summaries of individual data. **DONE**

Task 14: Conduct web-screening of 2,725 participants**. DONE**
a. Conduct 54-55 telephone interviews per week
b. Review interviews to determine eligibility for onsite screening
c. Schedule eligible participants for onsite screening appointments
d. Nurse practitioner continues to track menstrual cycle of eligible women

Task 15: Conduct onsite screening sessions for 506 participants. **IN PROGRESS**
a. Conduct 10–11 onsite screening sessions per week
b. Review test and interview results to determine eligibility for physical exam
c. Schedule eligible participants for physical examinations
d. Nurse practitioner continues to track menstrual cycle of all eligible women

Task 16: Nurse practitioner conducts physical examinations of 186 participants. **DONE**
a. Conduct 4 physical examinations per week
b. Review results of exam to determine eligibility (consulting with medical monitor)
c. Schedule eligible participants for BAES screening sessions
d. Continue to track menstrual cycle of all eligible women

Task 17. Conduct final medication-response sessions.

Task 18. Conduct final ERP sessions.

Task 19. Process remaining ERP data.

Task 20: Engineer adapts SCAN2 software for analysis of ERP data. **DONE**

Task 21: Complete all testing.

Task 22: Process final ERP data.

Task 23: Analyze ERP data. **IN PROGRESS**

a. For each task in the ERP battery, prepare grand-mean ERPs for each of the groups
b. For each task, conduct statistical analysis of ERP data, as detailed in the proposal
c. For each task, prepare tables and figures for publication and for final report to USAMRAA

Task 24: Prepare and submit manuscripts to peer-reviewed scientific journals. **IN PROGRESS**
a. Impulsivity (stop-signal task)
b. Novelty-seeking (novelty oddball task)
c. Reward salience (gambling task)

Problems

In the first year of the project, progress in obtaining HSRRB approval was slowed by the need to relocate our laboratory to space in a new building on the campus of the National Naval Medical Center. This relocation was required as a result of the Walter Reed Army Medical Center – National Naval Medical Center Base Realignment and Closure effort; and involved USU-sponsored renovations to accommodate electrophysiological recording and other aspects of this and our other research protocols. As noted in our first annual report, the laboratory was completely re-established. As we predicted, the new space accommodates this protocol more effectively than did the old space, and our progress was facilitated accordingly.

This year, the health screening of potential participants in this research was disrupted as a result of our nurse practitioner (NP) resigning unexpectedly. Because all participants must receive a physical exam by an NP, this issue imposed a delay on data collection. We identified a replacement NP, and submitted a collaborative agreement application for the NP to the Maryland Board of Nursing (as is required for NPs practicing in Maryland). While we awaited approval of the agreement, the NP found a higher-paying position and left the project, forcing us to start the process all over again. We identified a new NP, and submitted the collaborative agreement for her; however, due to a problem at the Board, approval of that agreement was took a full month longer than it should have. Her collaborative agreement was approved on January 15, 2010. Since that date, we have been screening (and testing) participants at a rapid pace. In all, this problem took four months to resolve.

Due to the substantial delays in data collection that occurred while this and the prior issues were being resolved, we determined that we would not be able to complete the tasks in the Statement of Work within the original project period. By managing the budget carefully, we retained sufficient funds to complete the project. Thus, we requested and were granted a one-year no-cost extension (NCE, during which we will complete the project.

Key Research Accomplishments

From the time the protocol was approved by the HSRRB (7/3/08), our focus has been on recruiting, screening, and testing participants, and on processing data obtained from these participants. Thus, the key research accomplishments are reflected in Table 1, which summarizes the number of participants who have completed each phase of the protocol. Data processing has largely kept pace with data collection.

The purpose of the web survey and the onsite health screening is to determine whether individuals meet the criteria for inclusion in the protocol. These criteria are designed to (1) minimize risk to participants and (2) maximize our ability to detect responder-group differences (i.e., to reduce heterogeneity). The purpose of the medication-response screening is to identify groups of individuals, using criteria developed in pilot studies in our laboratory, exhibiting distinct stimulant responses to *d*-amphetamine, who are then invited to participate in the ERP phase of the study. As is evident in Table 1, we have made significant progress.

Table 1. Participants completing each phase of the protocol

Phase of Study	June 2009	June 2010
Respondents to recruitment notices	1,962	5,935
Eligible for web survey	832	2,006
Completed web survey	593	1,503
Eligible for health screening	455	1,115
Completed health screening	198	596
Eligible for medication-response testing	137	431
Completed medication-response testing	66	170
Completed first ERP session (only)	11	14
Completed both ERP sessions	22	92

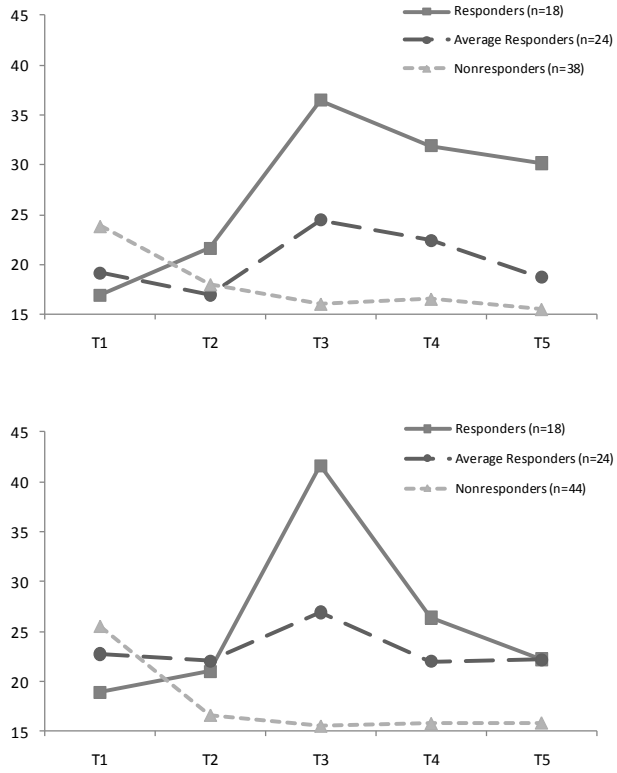

Figure 1. Mean scores on the Biphasic Alcohol Effects Scale (BAES) for women (top panel) and men (bottom panel) meeting criteria for inclusion in three responder groups. The BAES is administered before (T1) and four times after administration of 10-mg *d*-amphetamine, to identify a group of individuals with distinct types of stimulant response.

Reportable Outcomes

1. Gabbay, F. H., Duncan, C. C., & Williams, S. E. (2010). Brain indices of reward vary with behavioral control. Paper presented at annual meeting of *College on Problems of Drug Dependence*, Scottsdale, AZ, June, 2010.
2. Gabbay, F. H., Duncan, C. C., & Hall, E. C. Brain markers of risk for alcoholism. Paper presented at the third *Military Health Research Forum*, Kansas City, MO, August, 2009.
3. McDonald, C. G., Gabbay, F. H., Rietschel, J. C., & Duncan, C. C. Evidence for a new late positive ERP component in an attended novelty oddball task. *Psychophysiology*, in press.
4. Gabbay, F. H., Duncan, C. C., & McDonald, C. G. Brain markers of amphetamine preference: Event-related brain potential indices of novelty processing distinguish amphetamine choosers and nonchoosers. Submitted.
5. *A marker of risk and resilience for drug abuse: The brain's response to affective stimuli.* (FY10 Peer-Reviewed Medical Research Program, Congressionally Directed Medical Research Program (CDMRP), Principal Investigator: Frances H. Gabbay, Ph.D.)
6. *Defining an endophenotype: Novelty processing, amphetamine response, and genotype.* (Under review, National Institute on Drug Abuse, Principal Investigator: Frances H. Gabbay, Ph.D.)
7. *Brain indices of risk for PTSD after mild TBI* (Funded, CDMRP, Principal Investigator: Connie C. Duncan, Ph.D.)
8. *Predicting outcome after mild TBI: Brain indices of structure and function* (Funded, Department of Defense, Center for Neuroscience and Regenerative Medicine, Principal Investigator: Connie C. Duncan, Ph.D.)

Note: The papers listed as Items #3 and #4 do not report data collected under the auspices of this research grant. Rather, the papers are listed because they were completed during the project period and bear a conceptual relation to the current research, and because the work reported in the papers facilitated the development of the current protocol. The four applications for funding (#5 – #8) are listed because they benefited from the protocol development done for the current research. The pre-proposal listed as Item #5 was recently approved and a full application was invited; Items #7 and #8 have been approved for funding.

Conclusion

We are continuing to recruit, screen, and test participants. We have made important progress in data collection and processing, and have presented preliminary results at the third Military Health Research Forum in Kansas City, MO (September 1, 2009) and at the annual meeting of the College on Problems of Drug Dependence in Scottsdale, AZ (June 18, 2010).